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(54) IMMUNOMODULATOR, CELL ADHESION INHIBITOR, AND AGENT FOR TREATING AND PREVENTING AUTOIMMUNE DISEASES

(57) A 4H-1-benzopyran-4-one derivative of general formula [1], or a salt thereof exerts excellent effects of immunomodulation and cell adhesion inhibition, and is further expected to have the effect of relieving autoimmune diseases at a level comparable to that of steroids. Thus the compound of general formula [1] is useful in the treatment and prevention of autoimmune diseases fundamentally caused by immunopathy or abnormally accelerated cell adhesion, for example, chronic rheumatoid arthritis, systemic lupus erythematosus, sclerema, mixed connective tissue disease, polyarteritis nodosa, polymyositis/dermatomyositis, Sjögren's syndrome, Behcet's disease, multiple sclerosis, autoimmune diabetes, Hashimoto's disease, psoriasis, primary myxedema, pernicious anemia, serious adynamia, ulcerative colitis, chronic active hepatitis, autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura.

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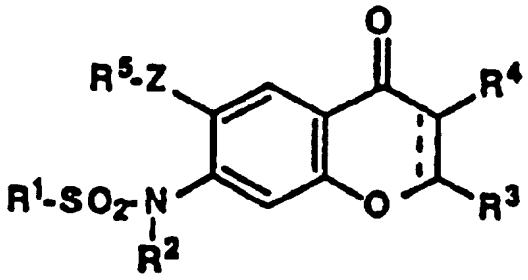


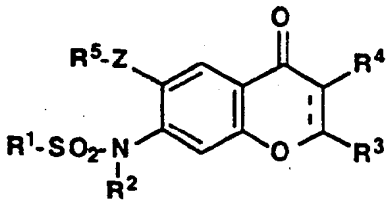
(1)

Description

The invention relates to an immunomodulating agent, a cell adhesion inhibiting agent and an agent for treating and preventing autoimmune diseases.

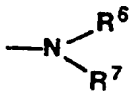
TECHNICAL FIELD

The present invention relates to an immunomodulating agent, a cell adhesion inhibiting agent and an agent for treating and preventing autoimmune diseases containing, as an active ingredient, a 4H-1-benzopyran-4-one derivative represented by the general formula [1] or a salt thereof:



[1]

wherein R^1 is an unsubstituted or halogen-substituted alkyl, alkenyl or aryl group; R^2 is a hydrogen atom or an alkyl or acyl group; R^3 is a hydrogen or halogen atom or a cyano, azido, carboxyl, hydroxyl, formyl or alkoxycarbonyl group or a substituted or unsubstituted alkyl, alkoxy, phenoxy, cycloalkyl, carbamoyl, amino or phenyl group; R^4 is a hydrogen or halogen atom, a nitro, cyano, carboxyl, acyl, hydroxyl or alkoxycarbonyl group, or a substituted or unsubstituted alkyl, alkoxy, alkylthio, phenylthio, alkynyl, alkenyl, sulfamoyl, alkanesulfinyl, alkanesulfonyl, amidino, phenyl or heterocyclic group or a group of the formula



or

where R^6 is a hydrogen atom, a hydroxyl, cyano or alkoxycarbonyl group or a substituted or unsubstituted alkyl, cycloalkyl, phenyl, amino,acyl, carbamoyl, alkanesulfonyl, iminomethyl or amidino group and R^7 is a hydrogen atom or a substituted or unsubstituted alkyl, alkoxy, phenyl,cycloalkyl or heterocyclic group, or R^6 and R^7, when taken together withthe nitrogen atom to which the two are bonded, form a 3- to 7-membered, substituted or unsubstituted heterocyclic group; R^5 is a substituted or unsubstituted phenyl, thienyl, furyl or pyridyl group; Z is an oxygen or sulfur atom or an imino group; and the broken line means a single or double bond.

BACKGROUND ART

The term "autoimmune disease" as used herein includes all of the diseases caused by an immune response such as an autoantibody or cell-mediated immunity to an autoantigen and the like. Examples of the diseases as described above include, for example, chronic rheumatoid arthritis, systemic lupus erythematosus, scleroderma, mixed connective tissue disease, polyarteritis nodosa, polymyositis/dermatomyositis, Sjögren'ssyndrome, Behcet's disease, multiple sclerosis, autoimmune diabetes, Hashimoto's disease, psoriasis, primary myxedema, pernicious anemia, myasthenia gravis, ulcerative colitis, chronic active hepatitis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura and the like.

In general for autoimmune diseases, it has been considered that the expression of mechanism symptoms is based on hereditary factors or environmental factors. That is to say, the initiation of the autoimmune disease is, for example,a virus infection and then an immunity disorder leads to autoimmune diseases. Up to now, symptomatic treatment using non-steroidal anti-inflammatory drugs has been mainly employed in order to control the inflammatory symptoms as a method of medical treatment for the diseases noted above. However, it is presently impossible to intrinsically cure, from the standpoint of side-effects, the disease by symptomatic treatment using non-steroidal anti-inflammatory drugs even if the effect of the drug has been favorably evaluated. Under such circumstances, a treatment method to intrinsically improve an aberrant immune system and immune enhancement based on an immunomodulating action and/or a cell adhesion inhibiting action is desireable.

As a medicament having an immunomodulating action, for example, D-penicillamine and Sulfasalazine have been described in Annual reports in medicinal chemistry (Annu. Rep. Med.Chem), Vol.21, pp. 201-210 (1986). It is also expected that a medicament which inhibitsthe appearance of cell adhesion molecules on the cell surface is useful as an agent for the treatment of autoimmune diseases. See example, Arthritis and Rheumatism, Vol 36, No. 2, pp.147-157(1993); and Clinical Immunology, Vol.26, No. 2, pp.190-197(1994).

A derivative of 4H-1- benzopyran-4-one or a salt thereof, which is represented by the general formula [1] is known and has anti-inflammatory analgesic, antipyretic, antiarthristic and antiallergic actions, [Japanese Patent Application Kokai No.2 (1990)-49778], and has a supressive effect on the production of interleukins 1 and 6, which is useful for prevention and treatment of diseases caused by abnormal production of interleukins 1 and 6, Journal of Pharamacobio Dynamics(J.Pharmacobio-Dyn.), Vol.15, pp.649-655(1992). However, it is not known that a derivative of 4H-1- benzopyran-4-one or a salt thereof is capable of improving abnormal immunity or aberrant enhancement of cell adhesion based on an immunomodulating and/or cell adhesion inhibiting action.

So far, D-penicillamine, Iobenzarit and the like have been used as immunomodulating agents or agents for autoimmune diseases. But there are few of these agents, and the effects against immunodeficiency are not sufficient. When these drugs have been used for long-term treatment, the effect of these drugs may be diminished. These drugs are never satisfactory as immunomodulating agents or agents for autoimmune diseases. Cell adhesion inhibitors have been researched for use as clinical drugs [Drug News & Perspectives, Vol.5, No. 6, pp. 331-337 (1992)]. Hence, the development of an agent which has a superior effect against immunodeficiency and a suppressive effect against aberrant enhancement of cell adhesion molecules, is expected to function a drug for treating and preventing autoimmune diseases.

It is an object of the present invention to provide an immunomodulating agent, a cell adhesion inhibiting agent and an agent for treating and preventing autoimmune diseases.

DISCLOSURE OF INVENTION

Under such circumstances, the present inventors have conducted extensive research to find that a 4H-1-benzopyran-4-one derivative represented by the general formula [1] or a salt thereof satisfies the desired object as described above, whereby the present invention has been completed.

The compounds in connection with the pharmaceutical agent are explained in detail below:

In the present specification, unless otherwise specified, terms have the following definitions .

The term "alkyl group" means preferably a C_{1-8} alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl or the like; the term "cycloalkyl group" means preferably a C_{3-8} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like; the term "alkenyl group" means preferably a C_{2-8} alkenyl group such as vinyl, allyl, 1-propenyl, 1-butenyl or the like; the term "alkoxy group" means preferably a -O-alkyl group (alkyl group has the same meanings as defined above); the term "acyl group" means preferably a formyl group, a C_{2-8} alkanoyl group such as acetyl, propionyl, butylyl or the like; alkoxyoxalyl group such as methoxalyl, ethoxalyl or the like; a C_{3-8} cycloalkanecarbonyl group such as cyclohexanecarbonyl or an aroyl group such as benzoyl or the like; the term "alkoxycarbonyl group"means a -COO-alkyl group (alkyl group has the same meanings as defined above); the term "alkoxycarbonylamino group" means a -NHCOO-alkyl group (alkyl group has the same meanings as defined above); the term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, an iodine atom or the like; the term "alkylthio group" means an -S-alkyl group (alkyl group has the same meanings as defined above); the term "alkanesulfinyl group" means preferably a C_{1-8} alkanesulfinyl group such as methanesulfinyl, ethanesulfinyl or the like; the term "alkanesulfonyl group" means preferably a C_{1-8} alkanesulfonyl group such as methanesulfonyl, ethanesulfonyl or the like; the term "aryl group" means preferably a phenyl, naphthyl or the like; the term "acylamino group" means a -NH-acyl group (acyl group has the same meanings as defined above); the term "alkylamino group" means a -NH-alkyl group (alkyl group has the same meanings as difined above); the term "dialkylamino group" means a -N(alkyl)$_2$ group (alkyl group has the same meanings as defined above); the term "haloalkyl group" means preferably a halo-C_{1-8} alkyl group such as chloromethyl, fluoromethyl, dichloromethyl, trifluoromethyl, dichloroethyl, trichloroethyl or the like; the term "alkynyl group" means preferably a C_{2-8} alkynyl group such as ethynyl, 2-propynyl or the like; the term "heterocyclic group" means preferably a 4- to 6-membered cyclic group containing at least on ehetero

atom selected from the group consisting of an oxygen atom, nitrogen atom and sulfur atom as the hetero atom forming the ring or a condensed cyclic group thereof, such as thienyl, furyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, benzthiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, quinolyl, isoquinolyl, pyrimidinyl, piperadinyl, pyrazinyl, pyridazinyl, 1,2,3,4-tetrahydroquinolyl, 1,2,4-triazinyl, imidazo [1,2-b] [1,2,4] triazinyl, pyrrolidinyl, morpholinyl, quinochidinyl or the like. Moreover, in the present specification, the term "lower alkyl group" means a lower alkyl group having 1 to 5 carbon atoms. In the general formula [1], when R^6 and R^7 form a 3- to 7-membered heterocyclic group with the nitrogen atom to which two are bonded, the heterocyclic group includes a nitrogen-containing heterocyclic group consisting of a 3- to 7-membered ring containing the nitrogen atom such as an azetidine-1-yl, a pyrrolidine-1-yl, a piperidine-1-yl, a pyrrole-1-yl and the like.

Additionally, the substituent of the alkyl, alkoxy, phenoxy, cycloalkyl, carbamoyl, amino and phenyl groups in R^3; the alkyl, alkoxy, alkylthio, phenylthio, alkynyl, alkenyl, sulfamoyl, alkanesulfinyl, alkanesulfonyl, amidino, phenyl and heterocyclic groups in R^4; the alkyl, cycloalkyl, phenyl, amino, acyl, carbamoyl, alkanesulfonyl, iminomethyl and amidino groups in R^6; the alkyl, alkoxy, phenyl, cycloalkyl and heterocyclic groups in R^7; the 3- to 7-membered heterocyclic groups which R^6 and R^7 form with the nitrogen atom to which the two are bonded and the phenyl, thienyl, furyl and pyridyl groups in R^5 may each be substituted by at least one substituent selected from the group consisting of halogen atoms, alkoxy groups, alkylthio groups, phenoxy group, carboxyl group, acyl groups, alkoxycarbonyl groups, carbamoyl group, sulfamoyl group, cyano group, alkanesulfonyl groups, hydroxyl group, mercapto group, acylamino groups, alkylamino groups, dialkylamino groups, alkyl groups, cycloalkyl groups, oxo group, nitro group, haloalkyl groups, amino group, phenyl group, alkoxycarbonylamino groups, hydroxyimino group and heterocyclic groups.

The salt of a 4H-1-benzopyran-4-one derivative of the general formula [1] includes a pharmaceutically acceptable salts, for example, salts with alkali metals such as sodium, potassium and the like; salts with alkaline earth metals such as calcium, magnesium and the like; ammonium salts; salts with organic amines such as triethylamine, pyridine and the like; salts with amino acids such as lysine, arginine, ornithine and the like; salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and the like; salts with organic carboxylic acids such as fumaric acid, maleic acid, malic acid, citric acid and the like; and salts with sulfonic acids such as methanesulfonicacid, p-toluenesulfonic acid, naphthalenedisulfonic acid and the like.

The 4H-1-benzopyran-4-one derivertive of the general formula [1] or a salt thereof includes isomers (including geometrical isomers and optical isomers), hydrates, solvates and cryctal forms.

The 4H-1-benzopyran-4-one derivative of the general formula [1] or a salt thereof can be producted by, for example, the processes described in the Japanese Patent Application Kokai No.2 (1990)- 249778.

The compounds of the present invention may be administered orally or parenterally in conventional manner in the form of capsules, powders, granules, pills, tablets, suspensions, emulsions, solutions, ointments, ampoules, syrups or suppositories. Further, the administration method, dose and number of administration times can be appropriately varied depending upon the age and symptom of a patient. Usually, the compound may be administered in several portions a day in a dose of about 5.0 to 1,000 mg per adult.

Among the 4H-1-benzopyran-4-one derivative compounds to be used as an active ingredient for the medicament, such as an immunomodulating agent, a cell adhesion inhibiting agent and an agent for treating and preventing autoimmune diseases, preferable are compounds of the general formula [1] wherein R^1 is a halogen-substituted or unsubstituted alkyl group; R^2 is a hydrogen atom ; R^3 is a hydrogen atom or a substituted or unsubstituted alkyl group; R^4 is a hydrogen atom, a carboxyl group, a substituted or unsubstituted alkylthio group, a substituted or unsubstituted acylamino group or a carbamoyl group; R^5 is a substituted or unsubstituted phenyl group; Z is an oxygen atom or an imino group; and the broken line means a double bond. More preferable are the compound wherein R^1 is an alkyl group; R^2 is a hydrogen atom; R^3 is a hydrogen atom; R^4 is a substituted or unsubstituted acylamino group; Z is an oxygen atom; R^5 is a substituted or unsubstituted phenyl group; Z is an oxygen atom; and the broken line means a double bond.

Among the compounds of the present invention of a 4H-1-benzopyran-4-one derivative to be used as an active ingredient for medicament such as an immunomodulating agent, a cell adhesion inhibiting agent and an agent for treating and preventing autoimmune diseases, representative compounds thereof are as follows:

1. 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.
2. 7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.
3. 6-(2,4-difluorophenoxy)-7-methylsulfonylamino-4H-1-benzopyran-4-one.
4. 3-carbamoyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.
5. 3-carbamoyl-2-methyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.
6. 3-(N-formyl-N-methyl)amino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.
7. 3-carboxy-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.
8. 3-methylthio-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.
9. 6-(2,4-difluorophenylamino)-3-formylamino-7-methylsulfonylamino-4H-1-benzopyran-4-one.
10. 3-carbamoyl-6-(2,4-difluorophenylamino)-7-methylsulfonylamino-4H-1-benzopyran-4-one.

11. 2-methyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one
12. 6-(2-fluorophenylamino)-3-formylamino-7-methylsulfonylamino-4H-1-benzopyran-4-one.

Next, the pharmacological activities of the compounds of the present invention to be used as the agent for an immunomodulating agent, cell adhesion inhibiting agent or agent for treating and preventing autoimmune diseases are explained by experiment. The test compound numbers used in the following experiments refer to the representative compound numbers as shown above.

Experiment 1 - The effect of the test compounds on the delayed-type hypersensitivity.

Pretreatment of a delayed-type hypersensitivity in potentiative immune mice with cyclophosphamide was carried out in accordance with the method of P.H.Lagrange et al., Journal of Experimental Medicine, Vol.139, pp.1529-1539(1974). In brief, BALB/c male mice (8 weeks old, 6 to 8 mice per group) were pretreated with intraperitoneal injection of 75mg/kg cyclophosphamide. Four days after the injection, 0.2 ml SRBC (sheep red blood cells) suspension ($5x10^7$ cells/ml) was intravenously sensitized. Three days after the sensitization, delayed-type hypersensitive responses were induced with intradermally injection of 0.05 ml SRBC suspension ($8x10^9$ cells/ml) to the left hind paw. After 24 hours, the mice were killed and both hind paws were cut off at the ankle to determine the weight of the paw . The SRBC-induced edema was measured as the difference between the left and right paw weights. The inhibitory percentage in paw edema produced by the compound treatment was expressed relative to the edema from the control mice. The test compounds were suspended in 0.5% carboxymethylcellulose (CMC) solution and were administered p.o. once a day for 5 days from 2 days prior to the sensitization. 0.5 % CMC solution instead of the test compounds was administered to the control mice.

The results are shown in Table 1.

TABEL 1

TEST COMPOUND	DOSAGE (mg/kg)	DELAYED-TYPE PAW EDEMA INHIBITIONS (%)
compound No.1	10	12
	30	27
	100	39
compound No.2	100	17
compound No.3	30	48
compound No.4	100	41
compound No.5	100	16
compound No.6	100	17
compound No.7	100	16
compound No.8	100	21
compound No.9	100	28
compound No.10	100	20
D-PENICILLAMINE	100	- 3
SULFASALAZINE	100	5
PREDNISOLONE	10	44

As shown in Table 1, the test compounds cause the suppression of a delayed-type hypersensitive response in potentiative immune mice. The suppressive activity of the test compounds is equal to that of prednisolone, and more than that of D-penicillamine or sulfasalazine.

Experiment 2-Effect of the test compounds on the hemolytic plaque forming cell (PFC) response.

BDF_1 male mice (6 to 7 mice per group) were intravenously in jected with $2x10^6$ or $2x10^8$ SRBC(sheep red blood cell). Four days after injection, the mice were killed and their spleens were excised. The number of hemolytic plaque forming cells (PFC) per spleen was dete rmined according to the method of Cunningham et al.Immunology, Vol.14, p559

(1968) on the basis of the method by N.K. Jerne et al., Science, Vol.140, p405 (1963). The percentage change in PFC number produced by the test compounds was expressed relative to the PFC number from the control group. The test compounds were suspended in 0.5 % CMC solution. The compounds were orally administered for 3 days from a day prior to injection. 0.5 % CMC solution instead of the test compounds was administered to the control mice.

The results are shown in Table 2.

TABLE 2

TREATMENT	DOSAGE (mg/kg)	PFC No./SPLEEN[a)] x10^3	PERCENTAGE OF CONTROL GROUP
2x10^8 cells Sensitization			
control group	-	240±8	100
compound No.1	1	231±18	963
	10	221±17	92
	100	129±20	54
PREDNISOLONE	10	17±3	7
2x10^6 cells Sensitization			
control group	-	4.87±0.53	100
compound No.1	1	7.06±1.17	145
	10	7.13±0.52	146
	100	5.40±0.49	111
PREDNISOLONE	10	3.97±0.78	81

a) Each value is the mean ± S.E.

As shown in Table 2, the test compounds showed the obvious diminution in the PFC numbers under the optimal dose of SRBC and augmentation under the suboptimal dose. These findings indicate that the test compounds exhibit either suppression under an abnormal enhanced immune response or potentiation under a low immune response, and that the test compounds have immunomodulatory activities.

Experiment 3- Effect of the test compounds on experimental allergic encep-haromyelitis.

Experimental allergic encepharomyelitis (EAE) is a prototype for cell-mediated autoimmune diseases, and has been widely used as an animal model of multiple sclerosis. According to the method described by Deguchi et al., Brain and Nerve, Vol.42, pp.391-397(1990), EAE was induced by using Lewis female rats (5 rats per group). In brief, rats were immunized s.c. in both hind paws with 0.1ml emulsion, composed of a 50% guinea pig spinal cord homogenate and an equal volume of complete Freund's adjuvant. Rats were observed daily from the day of immunizaton to day 18 for clinical symotoms of EAE and the scoring system used was as follows;

0:no symptoms
1:flaccid tail
2:incomplete paralysis of hind limb
3:complete paralysis of hind limb
4:quadriplegia or death

The test compound suspended in 0.5% CMC solution was orally administered once a day from the day (day 0) of immunization to day 13 and the animal was observed daily to day 18 for clinical symptoms of EAE.
0.5 % CMC solution instead of the test compound was administered to the control rats. The cumulative score of the symptoms for 18 days was obtained and the inhibitory percentage in the cumulative score produced by the test compound group was expressed relative to the cumulative score from the control group.

The results are shown in Table 3.

TABLE 3

TEST COMPOUND	DOSAGE (mg/kg)	INHIBITION(%) OF CLINICAL SCORE
compound No.1	1	21
	100	67
compound No.3	30	86
compound No.4	30	50
compound No.6	30	66
compound No.7	30	50
compound No.8	30	17
compound No.9	30	50
compound No.10	30	42
compound No.11	30	52
compound No.12	30	67
D-PENICILLAMINE	100	-10
SULFASALAZINE	300	1
PREDNISOLONE	10	52

As shown in Table 3, the test compounds cause the inhibition of the appearence and the severity of EAE. The test compounds are equal to thatof prednisolone, and more than that of D-penicillamine or sulfasalazine.

Experiment 4 - Effect of the compounds on the expression of cell adhesion molecule (very late antigen-4:VLA-4) in EAE rats.

VLA-4 is one of the cell adhesion molecules which may be involved in the migration of lymphocytes. The effect of the compounds on the expression of VLA-4 on lymphocytes from EAE rats was examined. According to the method described in Experiment 3, rats (7 rats per group) were immunized s.c. in both hind paw with 0.1ml emulsion, composed of a 50% guinea pig spinal cord homogenate and an equal volume of complete Freund's adjuvant.Ten days after immunization, blood was withdrawn by vena cava inferior in heparin from the rats anesthetized with ether. The leukocyte fraction was isolated from 5ml of the blood by density gradient centrifugation. $5x10^5$ of the leukocytes were suspended in 0.5 ml of phosphate buffered saline (PBS) containing 0.1 % bovine serum albumin and then reacted with 5 µl of mouse anti-rat VLA-4 antibo dy. After incubation at 4 °C for 1 hour, the cells were reacted with fluorescence isothiocyanate-conjugated sheep anti-mouse immunoglobulin for a further 30min. The cells were washed with PBS and were analyzed on flow cytometry.The lymphocyte population was isolated to construct a forward and 90° light scatter. The results were expressed as a percentage of VLA-4 positive cell number to the lymphocyte number.
The results are as shown in Table 4.

TABLE 4

TREATMENT	DOSAGE (mg/kg)	PERCENTAGE OF VLA-4 POSITIVE CELL (MEAN)
control group	-	29.9
compound No.1	100	12.0

As shown in Table 4, treatment with the test compound produce a decrease in the percentage of VLA-4 positive cells as compared with the control group.

Experiment 5 - Effect of the test compounds on the enhanced expression of cell adhesion molecule CD11b in HL-60 (human promyelocytic leukemia cell line) stimulated by phorbol myristate acetate (PMA).

CD11b is the α-chain of cell adhesion molucule Mac-1, which is expressed in the activation of monocytes. The effect of the test compounds on the expression of CD11b on monocytes, HL-60 cells was analyzed. In brief, $5x10^5$ HL-60 cells were suspended in 2 ml of RPMI-1640 containing 10 % fetal calf serum (FCS) in each well of a 12-well multiplate, and then PMA (3mg/ml final concentration) and the test compound were added to themedium. After incubation at 37°C for 24 hours in an atmosphere containig 5% CO_2, the cells were collected and was hed with PBS. $3x10^3$ HL-60 cells were resuspended in 300 µl PBS(containing 1% FCS) and incubated with 5 µl of phycoerythrin-conjugated mouse anti-human CD11b antibody. After 1 hour incubation at 4°C, the cells were washed with PBS. The cells were analyzed on flow cytometry, and the results were expressed as the enhanced percentage of CD11b positive cells in the treated group relative to the PMA-untreated group.
The results are as shown in Table 5.

TABEL 5

TEST COMPOUND	CONCENTRATION (µg/ml)	NUMBER OF MEASUREMENT	CD11b INCREASED RATE OF EXPRESSION (%) MEAN±S.E.
control	-	6	82.2±4.9
compound No.1	10	6	49.9±1.8

As shown in Table 5, the test compound suppresses the enhanced expression of CD11b positive cells by PMA stimulaton. Taken together with our study, the test compounds inhibit expression of and the enhanced expression of the adhesion molecules. These findings show that the compounds have the ability to inhibit cell adhesion molecules.

BEST MODE FOR CARRYING OUT THE PRESENT INVENTION

The following examples serve to illustrate and explain the pharmaceutical preparation of the present invention, but the preparation or the experiments of the present invention should not be limited thereto. In addition to the above, the compounds numbers used in the examples appearing hereinafter are in accord with each of the test compound numbers as described above.

Example 1

In conventional manner, there is prepared the desired hard gelatin capsule containing the following ingredients.

Compound 1 (test compound number 1)	50mg
Lactose	114.5mg
Cornstarch	20mg
Hydroxypropylcellulose	2mg
Light anhydrous silicic acid	1.5mg
Carboxymethylcellulose Calcium	10mg
Magnesium stearate	2mg
Total	200mg

Example 2

In conventional method, there is prepared the desired tablet containing the following ingredients.

Compound 1 (test compound number 1)	25mg
Lactose	49mg
Microcrystalline cellulose	36mg
Hydroxypropylcellulose	1mg
Carboxymethylcellulose	
Calcium	6.6mg
Magnesium stearate	1.2mg
Talc	1.2mg
Total	120mg

Example 3

In conventional method, there is prepared the desired tablet containing the following ingredients.

Compound 1 (test compound number 1)	50mg
Lactose	74mg
Microcrystalline cellulose	55mg
Hydroxypropylcellulose	2mg
Carboxymethylcellulose	
Calcium	15mg
Magnesium stearate	2mg
Talc	2mg
Total	200mg

Example 4

In conventional method, there is prepared the desired tablet containing the following ingredients.

Compound 1 (test compound number 1)	100mg
Lactose	49mg
Microcrystalline cellulose	55mg
Hydroxypropylcellulose	2mg
Carboxymethylcellulose	
Calcium	15mg
Magnesium stearate	2mg
Talc	2mg
Total	225mg

Example 5

In conventional method, there is prepared the desired tablet containing the following ingredients.

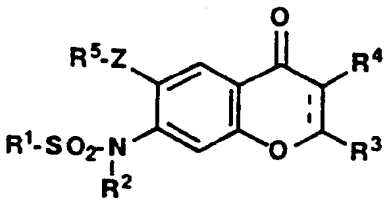
Compound 2 (test compound number 2)	200mg
Microcrystallinecellulose	100mg
Sodium starch glycolate	30mg
Magnesium stearate	3mg
Total	333mg

INDUSTRIAL APPLICABILITY

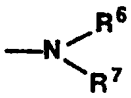
A 4H-1-benzopyran-4-one derivative of the general formura [1] or a salt thereof, exhibits excellent effects on immunomodulation and on cell adhesion inhibition, and is further expected to have the effect of relieving autoimmune diseases at a level comparable to that of steroids. Thus, the compound of the general formula [1] is useful in the treatment and prevention of autoimmune diseases fundamentally caused by immunopathy or unusually accelerated cell adhesion, for example, in chronic rheumatoid arthritis, systemic lupus erythematosus, scleroderma, mixed connective tissue disease,polyarteritis nodosa, polymyositis /dermatomyositis, Sjögren's syndrome, Behcet's disease, multiple sclerosis, autoimmune diabetes, Hashimoto's disease, psoriasis, primary myxedema, pernicious anemia, serious adynamia, ulcerative colitis, chronic active hepatitis, autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura.

Claims

1. An immunomodulating agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative represented by the following general formula or a salt thereof:



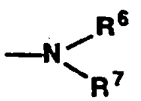
wherein R^1 is an unsubstituted or halogen-substituted alkyl, alkenyl oraryl group; R^2 is a hydrogen atom or an alkyl or acyl group; R^3 is a hydrogen or halogen atom or a cyano, azido, carboxyl, hydroxyl, formyl or alkoxycarbonyl group or a substituted or unsubstituted alkyl, alkoxy, phenoxy, cycloalkyl, carbamoyl, amino or phenyl group; R^4 is a hydrogen or halogen atom, a nitro, cyano, carboxyl, acyl, hydroxyl or alkoxycarbonyl group, or a substituted or unsubstituted alkyl, alkoxy, alkylthio, phenylthio, alkynyl, alkenyl, sulfamoyl, alkanesulfinyl, alkanesulfonyl, amidino, phenyl or heterocyclic group or a group of the formula



or

where R^6 is a hydrogen atom, a hydroxyl, cyano or alkoxycarbonyl group or a substituted or unsubstituted alkyl, cycloalkyl, phenyl, amino, acyl, carbamoyl, alkanesulfonyl, iminomethyl or amidino group and R^7 is a hydrogen atom or a substituted or unsubstituted alkyl, alkoxy, phenyl, cycloalkyl or heterocyclic group, or R^6 and R^7 , when taken together with the nitrogen atom to which the two are bonded, form a 3- to 7-membered, substituted or unsubstituted heterocyclic group; R^5 is a substituted or unsubstituted phenyl, thienyl, furyl or pyridyl group; Z is an oxygen or sulfur atom or an imino group; and the broken line means a single or double bond.

2. An immunomodulating agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 1, wherein R^1 is an unsubstituted or halogen-substituted lower alkyl, lower alkenyl or aryl group; R^2 is a hydrogen atom or an alkyl or acyl group; R^3 is a hydrogen or halogen atom or a cyano, azido, carboxyl, hydroxyl, formyl or alkoxycarbonyl group or a substituted or unsubstituted alkyl, alkoxy, phenoxy, cycloalkyl, carbamoyl, amino or phenyl group; R^4 is a hydrogen or halogen atom, a nitro, cyano, carboxyl, acyl, hydroxyl or alkoxycarbonyl group, or a substituted or unsubstituted alkyl, alkoxy, alkylthio, phenylthio, lower alkynyl, lower alkenyl, sulfamoyl, lower alkanesulfinyl, lower alkanesulfonyl, amidino, phenyl or heterocyclic group or a group of the formula



or

where R^6 is a hydrogen atom, a hydroxyl, cyano or alkoxycarbonyl group or a substituted or unsubstituted alkyl, cycloalkyl, phenyl, amino, acyl, carbamoyl, alkanesulfonyl, iminomethyl or amidino group and R^7 is a hydrogen atom or a substituted or unsubstituted alkyl, alkoxy, phenyl, cycloalkyl or heterocyclic group, or R^6 and R^7, when taken together with the nitrogen atom to which the two are bonded, form a 3- to 7-membered, substituted or unsubstituted heterocyclic group; R^6 is a substituted or unsubstituted phenyl, thienyl, furyl or pyridyl group; Z is an oxygen or sulfur atom or an imino group; and the broken line means a single or double bond.

3. An immunomodulating agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 1, wherein R^1 is an unsubstituted or halogen-substituted alkyl group; R^2 is a hydrogen atom; R^3 is a hydrogen atom or a substituted or unsubstituted alkyl group; R^4 is a hydrogen atom, a carboxyl group or a substituted or unsubstituted alkylthio or acylamino group or a carbamoyl group; R^5 is a substituted or unsubstituted phenyl group; Z is an oxygen atom or an imino group and the broken line means a double bond.

4. An immunomodulating agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 1, wherein R^1 is an unsubstituted or halogen-substituted lower alkyl group; R^2 is a hydrogen atom; R^3 is a hydrogen atom or a substituted or unsubstituted alkyl group; R^4 is a hydrogen atom, a carboxyl group or a substituted or unsubstituted alkylthio or acylamino group or a carbamoyl group; R^5 is a substituted or unsubstituted phenyl group; Z is an oxygen atom or an imino group; and the broken line means a double bond.

5. An immunomodulating agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 3 or 4, wherein R^3 is a hydrogen atom; R^4 is a substituted or unsubstituted acylamino group; Z is an oxygen atom.

6. An immunomodulating agent which comprises, as an active ingredient, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

7. An immunomodulating agent which comprises, as an active ingredient, 7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

8. An immunomodulating agent which comprises, as an active ingredient, 6-(2,4-difluorophenoxy)-7-methylsulfonylamino-4H-1-benzopyran-4-one.

9. An immunomodulating agent which comprises, as an active ingredient, 3-carbamoyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

10. An immunomodulating agent which comprises, as an active ingredient, 3-carbamoyl-2-methyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

11. 3-(N-formyl-N-methyl)amino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

12. An immunomodulating agent which comprises, as an active ingredient, 3-carboxy-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

13. An immunomodulating agent which comprises, as an active ingredient, 3-methylthio-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

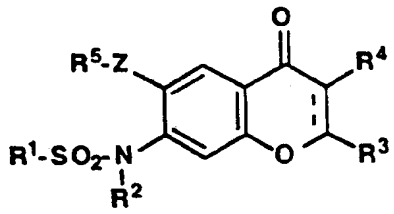
14. An immunomodulating agent which comprises, as an active ingredient, 6-(2,4-difluorophenylamino)-3-formylamino-7 methylsulfonylamino-4H-1-benzopyran-4-one.

15. 3-carbamoyl-6-(2,4-difluorophenylamino)-7-methylsulfonylamino-4H-1-benzopyran-4-one.

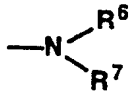
16. An immunomodulating agent which comprises, as an active ingredient, 2-methyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

17. An immunomodulating agent which comprises, as an active ingredient, 6-(2-fluorophenylamino)-3-formylamino-7-methylsulfonylamino-4H-1-benzopyran-4-one.

18. A cell adhesion inhibiting agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative represented by the following general formula or a salt thereof:



wherein R^1 is an unsubstituted or halogen-substituted alkyl, alkenyl or aryl group; R^2 is a hydrogen atom or an alkyl or acyl group; R^3 is a hydrogen or halogen atom or a cyano, azido, carboxyl, hydroxyl, formyl or alkoxycarbonyl group or a substituted or unsubstituted alkyl, alkoxy, phenoxy, cycloalkyl, carbamoyl, amino or phenyl group; R^4 is a hydrogen or halogen atom, a nitro, cyano, carboxyl, acyl, hydroxyl or alkoxycarbonyl group, or a substituted or unsubstituted alkyl, alkoxy, alkylthio, phenylthio, alkynyl, alkenyl, sulfamoyl, alkanesulfinyl, alkanesulfonyl, amidino, phenyl or heterocyclic group or a group of the formula

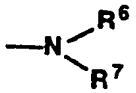


or

where R^6 is a hydrogen atom, a hydroxyl, cyano or alkoxycarbonyl group or a substituted or unsubstituted alkyl, cycloalkyl, phenyl, amino, acyl, carbamoyl, alkanesulfonyl, iminomethyl or amidino group and R^7 is a hydrogen atom or a substituted or unsubstituted alkyl, alkoxy, phenyl, cycloalkyl or heterocyclic group, or R^6 and R^7, when taken together with the nitrogen atom to which the two are bonded, form a 3- to 7-membered, substituted or unsubstituted heterocyclic group; R^6 is a substituted or unsubstituted phenyl, thienyl, furyl or pyridyl group; Z is an oxygen or sulfur atom or an imino group; and the broken line means a single or double bond.

19. A cell adhesion inhibiting agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 18, wherein R^1 is an unsubstituted or halogen-substituted lower alkyl, lower alkenyl or aryl group; R^2 is a hydrogen atom or an alkyl or aryl group; R^3 is a hydrogen or halogen atom or a cyano, azido, carboxyl, hydroxyl, formyl or alkoxycarbonyl group or a substituted or unsubstituted alkyl, alkoxy, phenoxy, cycloalkyl, carbamoyl, amino or phenyl group; R^4 is a hydrogen or halogen atom, a nitro, cyano, carboxyl, acyl, hydroxyl or alkoxycarbonyl group, or a substituted or unsubstituted alkyl, alkoxy, alkylthio, phenylthio, lower alkynyl, lower alkenyl,

sulfamoyl, lower alkanesulfinyl, lower alkanesulfonyl, amidino, phenyl or heterocyclic group or a group of the formula



or

where R^6 is a hydrogen atom, a hydroxyl, cyano or alkoxycarbonyl group or a substituted or unsubstituted alkyl, cycloalkyl, phenyl, amino, acyl, carbamoyl, alkanesulfonyl, iminomethyl or amidino group and R^7 is a hydrogen atom or a substituted or unsubstituted alkyl, alkoxy, phenyl, cycloalkyl or heterocyclic group, or R^6 and R^7 , when taken together with the nitrogen atom to which the two are bonded, form a 3- to 7-membered, substituted or unsubstituted heterocyclic group; R^5 is a substituted or unsubstituted phenyl, thienyl, furyl or pyridyl group; Z is an oxygen or sulfur atom or an imino group; and the broken line means a single or double bond.

20. A cell adhesion inhibiting agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 18, wherein R^1 is an unsubstituted or halogen-substituted alkyl group; R^2 is a hydrogen atom; R^3 is a hydrogen atom or a substituted or unsubstituted alkyl group; R^4 is a hydrogen atom, a carboxyl group or a substituted or unsubstituted alkylthio or acylamino group or a carbamoyl group; R^5 is a substituted or unsubstituted phenyl group; Z is an oxygen atom or an imino group; and the broken line means a double bond.

21. A cell adhesion inhibiting agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 18, wherein R^1 is an unsubstituted or halogen-substituted lower alkyl group; R^2 is a hydrogen atom; R^3 is a hydrogen atom or a substituted or unsubstituted alkyl group; R^4 is a hydrogen atom, a carboxyl group or a substituted or unsubstituted alkylthio or acylamino group or a carbamoyl group; R^5 is a substituted or unsubstituted phenyl group; Z is an oxygen atom or an imino group; and the broken line means a double bond.

22. A cell adhesion inhibiting agent which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 20 or 21, wherein R^3 is a hydrogen atom; R^4 is a substituted or unsubstituted acylamino group; Z is an oxygen atom.

23. A cell adhesion inhibiting agent which comprises, as an active ingredient, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

24. A cell adhesion inhibiting agent which comprises, as an active ingredient, 7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

25. A cell adhesion inhibiting agent which comprises, as an active ingredient, 6-(2,4-difluorophenoxy)-7-methylsulfonylamino-4H-1-benzopyran-4-one.

26. A cell adhesion inhibiting agent which comprises, as an active ingredient, 3-carbamoyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

27. A cell adhesion inhibiting agent which comprises, as an active ingredient, 3-carbamoyl-2-methyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

28. A cell adhesion inhibiting agent which comprises, as an active ingredient, 3-(N-formyl-N-methyl)amino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

29. A cell adhesion inhibiting agent which comprises, as an active ingredient, 3-carboxy-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

30. A cell adhesion inhibiting agent which comprises, as an active ingredient, 3-methylthio-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

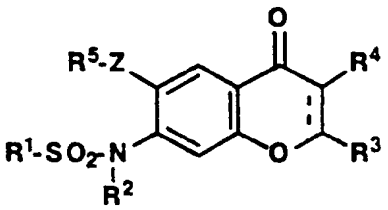
31. A cell adhesion inhibiting agent which comprises, as an active ingredient, 6-(2,4-difluorophenylamino)-3-formylamino-7-methylsulfonylamino-4H-1-benzopyran-4-one.

32. A cell adhesion inhibiting agent which comprises, as an active ingredient, 3-carbamoyl-6-(2,4-difluorophenylamino)-7-methylsulfonylamino-4H-1-benzopyran-4-one.

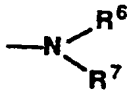
33. A cell adhesion inhibiting agent which comprises, as an active ingredient, 2-methyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

34. A cell adhesion inhibiting agent which comprises, as an active ingredient, 6-(2-fluorophenylamino)-3-formylamino-7-methylsulfonylamino-4H-1-benzopyran-4-one.

35. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative represented by the following general formula or a salt thereof:



wherein R^1 is an unsubstituted or halogen-substituted alkyl, alkenyl or aryl group; R^2 is a hydrogen atom or an alkyl or acyl group; R^3 is a hydrogen or halogen atom or a cyano, azido, carboxyl, hydroxyl, formyl or alkoxycarbonyl group or a substituted or unsubstituted alkyl, alkoxy, phenoxy, cycloalkyl, carbamoyl, amino or phenyl group; R^4 is a hydrogen or halogen atom, a nitro, cyano, carboxyl, acyl, hydroxyl or alkoxycarbonyl group, or a substituted or unsubstituted alkyl, alkoxy, alkylthio, phenylthio, alkynyl, alkenyl, sulfamoyl, alkanesulfinyl, alkanesulfonyl, amidino, phenyl or heterocyclic group or a group of the formula

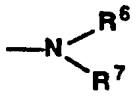


or

where R^6 is a hydrogen atom, a hydroxyl, cyano or alkoxycarbonyl group or a substituted or unsubstituted alkyl, cycloalkyl, phenyl, amino, acyl, carbamoyl, alkanesulfonyl, iminomethyl or amidino group and R^7 is a hydrogen atom or a substituted or unsubstituted alkyl, alkoxy, phenyl, cycloalkyl or heterocyclic group, or R^6 and R^7, when taken together with the nitrogen atom to which the two are bonded, form a 3- to 7-membered, substituted or unsubstituted heterocyclic group; R^5 is a substituted or unsubstituted phenyl, thienyl, furyl or pyridyl group; Z is an oxygen or sulfur atom or an imino group; and the broken line means a single or double bond.

36. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 35, wherein R^1 is an unsubstituted or halogen-substi-

tuted lower alkyl, lower alkenyl or aryl group; R^2 is a hydrogen atom or an alkyl or acyl group; R^3 is a hydrogen or halogen atom or a cyano, azido, carboxyl, hydroxyl, formyl or alkoxycarbonyl group or a substituted or unsubstituted alkyl, alkoxy, phenoxy, cycloalkyl, carbamoyl, amino or phenyl group; R^4 is a hydrogen or halogen atom, a nitro, cyano, carboxyl, acyl, hydroxyl or alkoxycarbonyl group, or a substituted or unsubstituted alkyl, alkoxy, alkylthio, phenylthio, lower alkynyl, lower alkenyl, sulfamoyl, lower alkanesulfinyl, lower alkanesulfonyl, amidino, phenyl or heterocyclic group or a group of the formula



or

where R^6 is a hydrogen atom, a hydroxyl, cyano or alkoxycarbonyl group or a substituted or unsubstituted alkyl, cycloalkyl, phenyl, amino, acyl, carbamoyl, alkanesulfonyl, iminomethyl or amidino group and R^7 is a hydrogen atom or a substituted or unsubstituted alkyl, alkoxy, phenyl, cycloalkyl or heterocyclic group, or R^6 and R^7, when taken together with the nitrogen atom to which the two are bonded, form a 3- to 7-membered, substituted or unsubstituted heterocyclic group; R^5 is a substituted or unsubstituted phenyl, thienyl, furyl or pyridyl group; Z is an oxygen or sulfur atom or an imino group; and the broken line means a single or double bond.

37. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 35, wherein R^1 is an unsubstituted or halogen-substituted alkyl group; R^2 is a hydrogen atom; R^3 is a hydrogen atom or a substituted or unsubstituted alkyl group; R^4 is a hydrogen atom, a carboxyl group or a substituted or unsubstituted alkylthio or acylamino group or a carbamoyl group; R^5 is a substituted or unsubstituted phenyl group; Z is an oxygen atom or an imino group and the broken line means a double bond.

38. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 35, wherein R^1 is an unsubstituted or halogen-substituted lower alkyl group; R^2 is a hydrogen atom; R^3 is a hydrogen atom or a substituted or unsubstituted alkyl group; R^4 is a hydrogen atom, a carboxyl group or a substituted or unsubstituted alkylthio or acylamino group or a carbamoyl group; R^5 is a substituted or unsubstituted phenyl group; Z is an oxygen atom or an imino group; and the broken line means a double bond.

39. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, a 4H-1-benzopyran-4-one derivative or a salt thereof according to Claim 37 or 38, wherein R^3 is a hydrogen atom; R^4 is a substituted or unsubstituted acylamino group; Z is an oxygen atom.

40. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

41. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

42. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 6-(2,4-difluorophenoxy)-7-methylsulfonylamino-4H-1-benzopyran-4-one.

43. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 3-carbamoyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

44. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 3-carbamoyl-2-methyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

45. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 3-(N-formyl-N-methyl)amino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

46. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 3-carboxy-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

47. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 3-methylthio-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

48. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 6-(2,4-difluorophenylamino)-3-formylamino-7-methylsulfonylamino-4H-1-benzopyran-4-one.

49. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 3-carbamoyl-6-(2,4-difluorophenylamino)-7-methylsulfonylamino-4H-1-benzopyran-4-one.

50. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 2-methyl-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one.

51. An agent for treating and preventing autoimmune diseases which comprises, as an active ingredient, 6-(2-fluorophenylamino)-3-formylamino-7-methylsulfonylamino-4H-1-benzopyran-4-one.

52. An agent for treating and preventing autoimmune diseases according to any one of Claims 35 to 51, wherein the autoimmune diseases are chronic rheumatoid arthritis, systemic lupus erythematosus, scleroderma, mixed connective tissue disease, polyarteritis nodosa, polymyositis / dermatomyositis, Sjögren's syndrome, Behcet's disease, multiple sclerosis, autoimmune diabetes, Hashimoto's disease, psoriasis, primary myxedema, pernicious anemia, myasthenia gravis, ulcerative colitis, chronic active hepatitis, autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP94/00585

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl[5] A61K31/35, A61K31/38, A61K31/40, A61K31/41, A61K31/44, A61K31/445, C07D311/24, C07D311/26,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl[5] A61K31/35, A61K31/38, A61K31/40, A61K31/41, A61K31/44, A61K31/445, C07D311/24, C07D311/26,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 2-49778 (Toyama Chemical Co., Ltd.), February 20, 1990 (20. 02. 90), Claim & US, A, 4,954,518 & GB, B, 2,210,879	1-52
A	J. Pharmacobio-Dyn., Vol. 15, No. 11, 1992, "Pharmacological studies on 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one(T-614), a novel antiinflammatory agent. 4th Communication: Inhibitory effect on the production of interleukin-1 and interleukin-6", P. 649-655	1-52

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
June 9, 1994 (09. 06. 94)	June 28, 1994 (28. 06. 94)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)